A Multicentre Phase II Study of AZD1775 plus Chemotherapy in Patients with Platinum-Resistant Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer.

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Primary objective:To evaluate the objective response rate (ORR) of AZD1775 in combination with gemcitabine, carboplatin, paclitaxel,or PLD in patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancerSecondary...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON46453

Source
ToetsingOnline

Brief title
AZD1775 + Chemotherapy to treat Ovarian, Fallopian Tube, Peritoneal Cancer.

Condition

- Other condition
- Reproductive and genitourinary neoplasms gender unspecified NEC
- Ovarian and fallopian tube disorders

Synonym
Ovarian Cancer Fallopian Tube Cancer Primary Peritoneal Cancer

Health condition

primaire buikvlieskanker

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: farmaceutisch bedrijf

Intervention

Keyword: Fallopian Tube Cancer, Ovarian Cancer, Primary Peritoneal Cancer

Outcome measures

Primary outcome

The primary endpoint of this study is ORR for the arms included in the efficacy assessment, defined as the proportion of patients achieving a complete or partial tumour response according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 (Eisenhauer et al 2009).

Secondary outcome

1. DoR, defined as the time from first documented tumour response until the date of documented progression or death from any cause

2.Treatment emergent adverse events (TEAEs), serious adverse events (SAEs), and deaths; clinically significant changes in safety-related laboratory parameters according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.03) and abnormal vital signs.

3.DCR, defined as the proportion of patients achieving a complete response (CR), partial response (PR), or stable disease (SD) according to RECIST v1.1 criteria.

4. GynaecologicCancer Intergroup (GCIG) CA-125 response, defined as the

proportion of patients achieving a 50% reduction in CA-125 levels from

baseline, if baseline level is *2 x the upper limit of normal (ULN) within 2

weeks prior to starting treatment. Response must be confirmed and maintained

for at least 28cdays

5.Plasma PK parameters of AZD1775 plus carboplatin, AZD1775 plus

paclitaxel,AZD1775 plus PLD, and AZD1775 plus gemcitabine

6.Plasma PK parameters of AZD1775 plus carboplatin, AZD1775 plus

paclitaxel,AZD1775 plus gemcitabine,and AZD1775 plus PLD

Study description

Background summary

This study is intended to understand the dose, dosage regimen, safety and tolerability of AZD1775 in combination with various chemotherapy agents and to assess its efficacy.The research hypothesis for the AZD1775 drug development programme is that administration of AZD1775 combined with chemotherapy in women with platinumresistant ovarian, fallopian tube, or primary peritoneal carcinoma experience improved progression-free survivalcompared to women receiving chemotherapy alone. This study is being conducted to understand the dose level, dosing schedule, safety, and tolerability of AZD1775 combined with chemotherapy agents such that they can be subsequently studied for improvement in efficacy.

Study objective

Primary objective:
To evaluate the objective response rate (ORR) of AZD1775 in combination with gemcitabine, carboplatin, paclitaxel,or PLD in patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer

Secondary Objectives:
1.To evaluate the duration of response (DoR) of AZD1775 in combination with gemcitabine, carboplatin,paclitaxel, or PLD
2.To evaluate the safety and tolerability of AZD1775 in combination with paclitaxel, gemcitabine, carboplatin or PLD in patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer

3.To evaluate the disease control rate (DCR) of AZD1775 in combination with carboplatin, paclitaxel,gemcitabine, or PLD in patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer
4.To evaluate the Cancer Antigen-125 (CA-125) response of AZD1775 in combination with carboplatin, paclitaxel,gemcitabine, or PLD in patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer.
5.To characterise the pharmacokinetics(PK)of AZD1775 plus carboplatin, AZD1775 plus paclitaxel, AZD1775 plus PLD, and AZD1775 plus gemcitabine
6.To assess the drug interaction between AZD1775 plus carboplatin, AZD1775 plus paclitaxel, AZD1775 plus gemcitabine, and AZD1775 plus PLD

Exploratory Objectives:
1. To identify genetic alterations in breast cancer genes 1 and 2 (BRCA1and BRCA2) and other relevant genes,including TP53,from analysis of archived or fresh tumour tissue collected at baseline, and to determine if the presence of a genetic alteration is predictive of clinical outcomes.
Molecular
2. To analyse changes in plasma circulating free tumour DNA (cfDNA) over time, from baseline, to restaging, and at disease progression. (This exploratory analysis will be reported separately from the Clinical Study Report [CSR].)
Blood
3. To obtain preliminary estimates of the overall survival (OS) and progression-free survival (PFS) of AZD1775 in combination with gemcitabine, paclitaxel,carboplatin, or PLD.
4.To collect and store deoxyribonucleic acid (DNA) for future research into genes/genetic variations that may influence PK orresponse to AZD1775 (i.e., absorption, distribution, metabolism, excretion, safety and efficacy) and/or susceptibility to the development of cancers.

Study design

This is an open-label, four-arm lead-in safety and efficacy study in which AZD1775 will be combined in four separate treatment arms as follows: AZD1775 plus gemcitabine(Arm A); AZD1775 plus weekly paclitaxel(Arm B); AZD1775 plus carboplatin (Arm C); and AZD1775 plus PLD (Arm D). A subset of patients will be evaluated for the safety assessment of each treatment arm (see Section 7.2.3.1 protocol).
The AZD1775 plus paclitaxel arm (Arm B) will enrol approximately 30 additional patients at selected sites as part of a further efficacy evaluation based on emerging data that suggests clinical activity. The AZD1775 plus carboplatin arm (Arm C) will enrol approximately 23 patients overall at selected sites as part of a further efficacy evaluation based on emerging data that suggests clinical activity. To further optimise the dosing schedule of AZD1775 in Arm C, a safety expansion arm (referred to as Arm C2) of approximately 12 additional patients will be enrolled at selected sites to receive carboplatin AUC 5 IV on Day 1 of a 21 day cycle in combination with AZD1775 BID for 2.5 days per dosing week

(QW), on Weeks 1 (D1-3), 2 (D8-10) and 3 (D15-17), or on Weeks 1 (D1-3) and 2 (D8-10) (2 weeks on followed by 1 week off). These additional weeks of AZD1775 dosing are meant to explore emerging pre-clinical and clinical data that suggest that prolonged AZD1775 exposure may increase the clinical activity. Initially, 6 patients will be enrolled in a 3-weekly AZD1775 dosing cycle; if 1 patient or less experiences a DLT during Cycle 1, then an additional 6 patients will be enrolled for a total of 12 patients. However, if 2 or more of the first 6 patients experience a DLT then the AZD1775 dosing may be modified to 2 weeks on followed by 1 week off. All decisions which include but are not limited to cohort dosing, dose escalation or de-escalation will be reviewed by the Safety Review Team (SRT). Modified PK assessments will be obtained to harmonise and accommodate the investigation of alternative dose levels and/or schedules.

Intervention

This is an open-label, four-arm lead-in safety and efficacy study in which AZD1775 will be combined in four separate treatment arms as follows: AZD1775 plus gemcitabine(Arm A); AZD1775 plus weekly paclitaxel(Arm B); AZD1775 plus carboplatin (Arm C); and AZD1775 plus PLD (Arm D). A subset of patients will be evaluated for the safety assessment of each treatment arm (see Section 7.2.3.1 protocol).
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Study burden and risks

For all details, please refer to study schedule on page 44-55 of the protocol (version 8, 19Jun2017). Also, see E4, E6, E9 for burden and possible risks.

Contacts

Public
Astra Zeneca

Karlebyhus, Astraallen n.v.t.
Södertälje S-151 85
SE
Scientific
Astra Zeneca

Karlebyhus, Astraallen n.v.t.
Södertälje S-151 85
SE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Has read and understands the informed consent form (ICF) and has given written consent.;2. Histologic or cytologic diagnosis of epithelial ovarian, fallopian tube, or primary peritoneal cancer.;3. Progressed within 6 months of completing at least 4 cycles of a first-line platinum-containing regimen for Stage III/IV disease. Patients with refractory disease (progression during platinum-containing therapy) are ineligible.;4. No more than 2-4 prior treatment regimens for Stage III/IV disease, defined as investigational, chemotherapy, hormonal, biologic, or targeted therapy.;5. Prior doxorubicin (or other anthracycline) at a cumulative dose of * 360 mg/m² or cumulative epirubicin dose of * 720 mg/m² (calculated using doxorubicin equivalent doses: 1 mg of doxorubicin <= 1 mg PLD <= 0.3 mg mitoxantrone <= 0.25 mg idarubicin). Subjects without any prior anthracycline exposure can also be included (applies to Arm D only).;6. At least 1 measurable lesion according to RECIST v1.1.;7. Any prior palliative radiation therapy must be completed at least 7 days prior to start of study treatment and patients must have recovered from any acute adverse effects prior to start of study treatment. ;8. ECOG Performance Status (PS) score of 0 - 1.;9. Baseline Laboratory Values within 7 days of starting study drugs:
a) ANC *1500/*L
b) HgB * 9 g/dL with no blood transfusions in the past 28 days
c) Platelets * 100,000/*L

d) ALT & AST * 3 x ULN or * 5 x ULN if known hepatic metastases
e) Serum bilirubin within normal limits (WNL) or *1.5 x ULN in patients with liver metastases; or total bilirubin * 3.0 x ULN with direct bilirubin WNL in patients with well documented Gilbert*s Syndrome.
f) Serum creatinine *1.5 x ULN OR measured creatinine clearance (CrCl) * 45 mL/min by the Cockcroft-Gault method.;10. Left ventricular ejection fraction (LVEF) WNL of the institution, as determined by multiple uptake gated acquisition (MUGA) or echocardiography (ECHO) (applies to Arm D only).;11. Female patients who are not of childbearing potential and fertile female patients of
childbearing potential who agree to use adequate contraceptive measures from 2 weeks prior to the study and until 1 month after study treatment discontinuation, who are not breastfeeding, and who have a negative serum or urine pregnancy test within 3 days prior to start of study treatment;12. Predicted life expectancy * 12 weeks;13. Must be *18 years of age.;14. Willingness and ability to comply with study and follow-up procedures.

Exclusion criteria

1. Participation in another clinical investigational study within the previous 28 days. ;2. Use of a study drug (approved or investigational drug therapy) * 21 days or 5 half-lives (whichever is shorter) prior to the first dose of study treatment. For study drugs for which 5 half-lives is * 21 days, a minimum of 10 days between termination of the study drug and administration of study treatment is required.;3. Major surgical procedures * 28 days of beginning study treatment, or minor surgical
procedures * 7 days. No waiting required following port-a-cath placement, or any other central venous access placement.;4. No other chemotherapy, immunotherapy, hormonal anti-cancer therapy, radiotherapy (except for palliative local radiotherapy), biological therapy or other novel agent is permitted while the patient is receiving study medication. ;5. Grade >1 toxicity from prior therapy (except alopecia or anorexia).;6. Known malignant CNS disease other than neurologically stable, treated brain metastases * defined as metastasis having no evidence of progression or haemorrhage after treatment for at least 2 weeks (including brain radiotherapy). Must be off any systemic corticosteroids for the treatment of brain metastases for at least 14 days prior to enrolment.;7. Any prescription or non-prescription drugs or other products (i.e. grapefruit juice) known to be sensitive CYP3A4 substrates or CYP3A4 substrates with a narrow therapeutic index, or to be moderate to strong inhibitors or inducers of CYP3A4, which cannot be discontinued 2 weeks prior to Day 1 of dosing and withheld throughout the study until 2 weeks after the last dose of study drug.

8. Any of the following cardiac diseases currently or within the last 6 months as defined by New York Heart Association (NYHA) * Class 2:
a) Unstable angina
b) Congestive heart failure
c) Acute myocardial infarction
d) Conduction abnormality not controlled with pacemaker or medication
e) Significant ventricular or supraventricular arrhythmias (patients with chronic rate

controlled atrial fibrillation in the absence of other cardiac abnormalities are eligible).;9. AZD1775 should not be given to patients with a history of Torsades de pointes unless all risk factors that contributed to Torsades have been corrected. AZD1775 has not ben studied in patients with ventricular arrhythmias or recent myocardial infarction.;10. Corrected QT interval (QTc) >470 msec at study entry or congenital long QT syndrome. QTc interval will be calculated using Fridericia's formula (per institutional standards) obtained from 3 ECGs performed 2-5 minutes apart at study entry.

11.Pregnant or lactating.;12. Serious active infection upon enrolment, or other serious underlying medical condition that would impair the patient's ability to receive study treatment. ;13. Presence of other active cancers, or history of treatment for invasive cancer within the last 3 years. Patients with Stage I cancer who have received definitive local treatment within the last 3 years, and whom are considered unlikely to recur, are eligible. All patients with previously treated in-situ carcinoma (i.e., non-invasive) are eligible, as are patients with prior non-melanoma skin cancers.;14. Psychological, familial, sociological, or geographic conditions that do not permit compliance with the protocol.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-01-2018
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	AZD1775 capsule 100 mg
Generic name:	AZD1775 capsule 100 mg

Product type:	Medicine
Brand name:	AZD1775 capsule 25 mg
Generic name:	AZD1775 capsule 25 mg
Product type:	Medicine
Brand name:	several manufacturers
Generic name:	paclitaxel
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	03-10-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	14-12-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	22-03-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	30-03-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	21-08-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	05-09-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO	

Date:	26-04-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2015-000886-30-NL
ClinicalTrials.gov	NCT02272790
CCMO	NL62988.031.17